Application No. 10/736,188
Amendment dated June 2, 2008
Reply to Office Action of April 3, 2008

Docket No.: ALEX-P03-060

REMARKS

Claims 19, 21, 43, and 52-53 are pending in the subject application. Claims 44-45, 54-55, and 71-78 are withdrawn. Claims 71-78 have been canceled, without prejudice. Claim 19 has been amended. The claim amendments are fully supported by the specification and introduce no new matter. In particular, support for the amendments to claim 19 can be found, for example, at paragraphs [0086], [0138], and [0139] of the published application (US Publication No. 2004/0198661).

Amendment or cancellation of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Specification

The Office maintained the objection to the specification related to demarcation of trademarks. As requested by the Examiner, further amendments to the specification have been made to properly demarcate the trademarks. Withdrawal of the objection is requested.

Definiteness—35 USC § 112, second paragraph

The Office maintains its assertion that claims 19, 21, 43, and 52-53 are indefinite because of the use of the term "OX-2/CD200" or "CD200." The Office seems to draw this conclusion based on a search of "CD200" which identified two isoforms of OX-2/CD200 polypeptide of varying lengths. Therefore, the Office appears to require Applicants to specify a particular sequence designation for the OX-2/CD200 protein that would bind the antibody or antigen-binding fragment recited in the claims. Otherwise, the Office contends, it cannot be determined to which structurally and

functionally distinct proteins of OX-2/CD200 the antibody must bind. Applicants respectfully disagree with this rejection.

MPEP §2173.02 states that the essential inquiry pertaining to requirement for definiteness of 35 USC §112, second paragraph, is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Contrary to the Examiner's assertion, a skilled practitioner in the art would readily recognize the particular OX-2/CD200 to which the specification refers in view of the disclosure of the instant application and the teachings of the prior art. In particular, the specification and the references incorporated therein unambiguously refer to the OX-2/CD200 antigen to which the antibody binds. Particularly, the specification at section [0009] of published application US 2004/0198661A1 cites Gorczynski et al. (*Transplantation* 65:1106-1114, 1998) in the context of the immune suppressive effects of OX-2/CD200. Gorczynski et al., incorporated by reference in its entirety, disclose the full sequence of OX-2/CD200 (see, for example, Figure 5 of Gorczynski et al.). Therefore, it would be clear to one of ordinary skill in the art to which variant of OX-2/CD200 the specification refers.

Furthermore, claim 19 has been amended to define the OX-2/CD200 of interest, specifically the species upregulated on the surface of CLL cells in a patient afflicted with CLL. As clearly outlined in the subject application, the OX-2/CD200 antibody recited in the pending claims was produced by immunizing rabbits with whole peripheral blood mononuclear cells (PBMC) isolated from CLL patients, and were further enriched for CLL cell surface-specific binding by several rounds of positive-negative selection (see Example 2 beginning at [0097]). Briefly, antigen-negative cells such as TF-1 or normal human B cells were used as "absorber cells" to eliminate phage that bound non-specifically as well as phage that bound to "common" antigens present on both absorber cells and CLL cells, ensuring an antibody product that is highly specific to antigen expressed on CLL cells. Then, of the candidate scFv antibodies, those that stained more brightly on PBMC from CLL patients as compared to those from normal donors were selected and used to

immunoprecipitate the lysates from cell-surface biotinylated CLL cells. Such a method identified OX-2/CD200, which was overexpressed 3 to 6-fold particularly on the surface of a subset of CLL tumors. Clearly, one of skill in the art would readily recognize that the claim is directed to OX-2/CD200 that is upregulated on the surface of CLL tumors.

Accordingly, in view of the amendment and reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Written Description—35 USC § 112, first paragraph

Claims 19, 21, 43, and 52-53 remain rejected as allegedly failing to comply with the written description requirement. The Examiner asserts that OX-2/CD200 has multiple immune suppressing effects, such as downregulation of IFN-γ or IL-2, or upregulation of IL-10. The Examiner appears to allege that the specification demonstrates the use of scFv-9 antibody in the reversal of just one type of OX-2/CD200 immune suppressive effect, particularly the downregulation of IL-2 and IFN-γ. Therefore, it is alleged that one of skill could not recognize which OX-2/CD200 immune suppressive effects could be inhibited by the scFv-9 antibody *other* than an immune suppressive effect characterized by the downregulation of IL-2 or IFN-γ. Furthermore, it is alleged that because "human OX-2/CD200" represents multiple structurally distinct polypeptides, a skilled artisan could not determine which OX-2/CD200 polypeptide is referred to by the claims and, therefore, the nature of the antibody is also ambiguous.

Applicants respectfully disagree with the Examiner's rejection. However, solely to expedite prosecution of the subject application, Applicants have amended claim 19 to specify the type of OX-2/CD200 immune suppressive effect. As acknowledged by the Examiner, the specification provides sufficient written description for the method of using an antibody or antigen-binding fragment that binds OX-2/CD200 to inhibit the downregulation of IFN-γ or IL-2. As noted by the Examiner (p.10, lines 4-6 of the current Office Action), and as also presented by Applicants in the Response dated December 27, 2007, the method of claim 19 is fully described by the specification for all antibodies, and not just scFv-9, that bind to the particular OX-2/CD200. Additionally, the

Examiner raises again the issue addressed in the previous section relating to the ambiguity of OX-2/CD200. For reasons stated in the previous section, one of ordinary skill in the art would clearly recognize the particular variant of OX-2/CD200 to which the recited antibody binds. Reconsideration and withdrawal of this rejection are respectfully requested.

Enablement—35 USC § 112, first paragraph

Claims 19, 21, 43, and 52-53 remain rejected as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

The Examiner maintains that one of skill in the art would not conclude that the *in vitro* result in which an scFv-9 antibody inhibits the down-regulation of IL-2 or IFN-gamma is reasonably predictive of the genus of anti-OX-2/CD200 antibodies that have an *in vivo* anti-tumor effect. Applicants respectfully remind the Examiner that no showing of treatment of a human being is required to support operability of claims directed to methods of treating disease. See, e.g., *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). Moreover, *in vivo* data is **not** required to enable an *in vivo* use. Rather, use of *in vitro* data may be sufficient to show the required utility (see *Cross v. Iizuka*, 753 F.2d 1040, 1046-1047 (Fed. Cir., 1985) *citing Nelson v. Bowler*, 626 F.2d 853 (Fed. Cir. 1980)). An *in vitro* model or animal based evidence that is reasonably predictive is sufficient (*In re Brana*). A rigorous or an invariable exact correlation between *in vitro* utility and *in vivo* activity is **not** required for purposes of enablement (see MPEP 2164.02 *citing Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985)).

As amended, claim 19 is directed to a method of inhibiting the down-regulation of IL-2 or IFN-gamma in a CLL patient. As detailed in Applicants' previous Response, the instant specification provides working examples showing that anti-OX-2/CD200 antibodies are capable of restoring the Th1 cytokine profile. In particular, the Examiner's attention is directed to Example 3 at paragraphs [0129]-[0139] which discloses the results of a mixed lymphocyte reaction which was used to evaluate the effects of IL-2 and IFN-gamma production. The Example discloses that the presence of OX-2/CD200 transfected but not untransfected cells results in a down-regulation of IL-2

and IFN-gamma. Addition of an anti-CD200 antibody at 30 μg/ml fully restored the Th1 response, indicating that the antibody blocked interaction of OX-2/CD200 with its receptor (see e.g., paragraph [00138]). Although this is an *in vitro* assay, it replicates what occurs *in vivo*, i.e., there are interactions between CD200 and its receptors on lymphocytes which modulate the immune response. Prevention of such interactions, such as by binding an antibody to OX-2/CD200, would therefore be expected to similarly affect the *in vivo* immune response. As such, a skilled artisan would reasonably expect, in the absence of evidence to the contrary, that the same treatment would have the same effect in CLL patients *in vivo*. Accordingly, Applicants submit that the instant application provides sufficient disclosure and working examples that would enable one of skill in the art to carry out the claimed method of inhibiting the down-regulation of IL-2 or IFN-gamma in a CLL patient. Since the initial burden is on the Examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. In contrast, the Office merely relies on references such as Zips et al. and Gura et al. to broadly assert lack of correlation and predictability in extrapolating *in vitro* methods to *in vivo* applications in the field of cancer therapy in general, and provides neither scientific reasoning nor relevant references to buttress its argument, thus failing to meet the initial burden required by MPEP to support its argument of non-enablement.

Applicants further point out, pursuant to MPEP 2164.02:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Evidently, based on the above passage, either an *in vitro* or an *in vivo* model is sufficient to support the claimed methods, as long as there is correlation between the model and the claimed use. The Examiner seems to have misinterpreted the standard as requiring both *in vitro* and *in vivo* correlation, and requires Applicants to provide an *in vivo* model, even in the presence of a correlating *in vitro* model. This is clearly inconsistent with the Office policy and the MPEP guideline set forth above. If Applicants were required to provide both *in vitro* and *in vivo* data, then *in vitro* data would be irrelevant, as such data alone would never satisfy the standard of the Examiner.

Additionally, as set forth above in the MPEP guideline, Applicants request the Examiner to consider the state of the prior art and the particular *in vitro* CLL model of the present specification. At the time of filing, reversing the cytokine shift to a Th1 profile (inhibition of IL-2 and IFN-gamma down-regulation) has been demonstrated to augment anti-tumor effects of T cells (see e.g., paragraph [0008]). "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Applicants' *in vitro* system described in the specification provides a demonstrated and recognized model in which reversing the cytokine shift to a Th1 profile can augment anti-tumor effects of T cells. The Examiner has not provided any evidence that such a model system indeed fails to be reasonably predictive in an *in vivo* system. The Examiner has pointed to references expressing a desire for better models for cancer therapy. However, as stated previously, the desire for better models does not undercut the value of the current recognized model systems.

In further support of the assertion that one of skill in the art could not predict whether the recited antibodies would be effective to treat human CLL patients with upregulated OX-2/CD200, the Examiner relies on Chen et al. The Examiner notes that only antibodies that bind to the N-terminal region of OX-2/CD200 have the ability to inhibit the down-regulation of IL-2 caused by OX-2/CD200, while antibodies that specifically bind in the C-terminal region do not have this ability. The Examiner appears to assert that, because of such variability, it would require undue burden and experimentation before one of skill in the art could reasonably predict whether such

antibodies would be effective to treat human CLL patients with upregulated OX-2/CD200. To the contrary, a skilled practitioner in the field would not have been burdened with such undue experimentation. First, this finding simply confirms that the N-terminus of OX-2/CD200 plays an important role in binding its receptor, CD200R—a known fact in the field. Applicants remind the Examiner of the way in which the recited antibodies were generated. As described above, whole cells from CLL patients were used to immunize rabbits, after which OX-2/CD200 was identified as the antigen recognized by an scFv antibody, specifically scFv-9. Typical of type I transmembrane proteins, the portion of OX-2/CD200 exposed on the cell-surface is its N-terminus. It would be clear to one of skill in the art, then, that the N-terminus of OX-2/CD200 is indeed the area that confers its activity. As such, there would be no logical reason for a skilled practitioner to engage in undue experimention with any part of the C-terminus.

Chen et al. further identify the particular epitopes in the N-terminus critical for its interaction with CD200R. In light of these findings, it is to be expected that certain epitopes in the N-terminus are more important for the CD200-CD200R interaction and, as such, certain antibodies would be expected to be more efficacious than others. The Examiner appears to assert, then, that it would require undue experimentation before one of skill in the art could predict which one of such antibodies would be effective to treat human CLL patients. According to MPEP 2164.06, however, " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). In this case, Applicants submit that the instant application provides extensive guidance that clearly enables one of ordinary skill in the art to carry out the claimed methods. For example, the specification discloses that OX-2/CD200 is upregulated on CLL cells (see e.g., Figure 8c and paragraphs [0120]-[0123] of the published application), and also teaches that subjects suffering from CLL may be screened to determine whether the subject has upregulated CD200 (see e.g., paragraph [0038]). CDR sequences for several anti-OX-2/CD200 antibodies are provided (see e.g., Figure 9B). In addition, the specification provides guidance for testing whether a particular antibody can restore the Th1 response in a mixed lymphocyte assay (see

e.g., paragraphs [0135]-[0139]). Reversal of the cytokine shift to a Th1 profile has been demonstrated to augment the anti-tumor effects of T cells (see e.g., paragraph [0008]). Therefore, the specification clearly provides sufficient guidance with respect to the direction in which the experimentation should proceed.

Finally, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Based on the above remarks, Applicants submit that the currently claimed methods meet the enablement requirements under 35 USC §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 19, 21, 43, and 52-53 are provisionally rejected on the basis of obviousness-type double patenting over claims 50-54 and 70 of copending Application No. 10/379,151. Applicants note that claims 50-54 have been cancelled in copending Application No. 10/379,151. Applicants request that the Examiner hold the provisional rejections made under the judicially created doctrine of obviousness-type double patenting in abeyance until otherwise allowable subject matter is identified in the instant application. Once allowable subject matter has been identified, Applicants will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time.

Written Description—35 USC § 112, first paragraph

Claims 19, 21, 43, and 52-53 are rejected as allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that the specification does not provide support for "an immune-suppressing effect of OX-2/CD200" as recited in claim 19. Applicants respectfully disagree. However, solely to expedite prosecution of the subject application, claim 19 has been amended to recite "the downregulation of IL-2 or IFN-gamma", which is fully supported throughout the specification. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants believe no fees are due with this response other than those specifically itemized on the enclosed fee transmittal. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, from which the undersigned is authorized to draw under Order No. ALEX-P03-060.

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Respectfully submitted,

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